ORIGINAL ARTICLE

A consensus approach to wound care in epidermolysis bullosa

Elena Pope, MD, MSc,[a] Irene Lara-Corrales, MD, MSc,[a] Jemima Mellerio, MD,[c] Anna Martinez, MD,[c] Gregory Schultz, MD, PhD,[d] Robert Burrell, PhD,[e] Laurie Goodman, BSc, MN,[f] Patricia Coutts, BSc,[f] John Wagner, MD,[g] Upton Allen, MD,[b] and Gary Sibbald, MD, MSc[h]

Toronto, Ontario, and Edmonton, Alberta, Canada; London, United Kingdom; Gainesville, Florida; and Minneapolis, Minnesota

Background: Wound care is the cornerstone of treatment for patients with epidermolysis bullosa (EB); however, there are currently no guidelines to help practitioners care for these patients.

Objectives: The objective of this study was to generate a list of recommendations that will enable practitioners to better care for patients with EB.

Methods: An expert panel generated a list of recommendations based on the best evidence available. The recommendations were translated into a survey, and sent to other EB experts to generate consensus using an online-based modified Delphi method. The list was refined and grouped into themes and specific recommendations.

Results: There were 15 respondents (45% response rate), with significant experience in the EB field (>10 years [67%]). Respondents included physicians (67%), nurses (17%), and allied health professionals (7%). There was more than 85% agreement for all the proposed items. These were further refined and grouped into 5 main themes (assessment and management of factors that impair healing, patient-centered concerns, local wound care, development of an individualized care plan, and organizational support) and 17 specific recommendations.

Limitations: There is a paucity of scientific evidence with most recommendations based on expert opinion.

Conclusions: These recommendations will provide practitioners with a framework for caring for these patients. Additional scientific research including effectiveness studies for everyday practice and expert consensus, may further refine these recommendations. (J Am Acad Dermatol 10.1016/j.jaad.2012.01.016.)

Key words: consensus; epidermolysis bullosa; guidelines; wound care.

Epidermolysis bullosa (EB) is a group of inherited diseases characterized by mechanical fragility of the skin and mucous membranes. There are 4 subtypes of EB resulting from structural protein gene mutations at the cutaneous basement membrane zone or the relatively rare, suprabasal cell-cell adhesion desmosomal proteins.[1] The severity of mucocutaneous and other organ disease varies considerably between EB types, and is largely

Abbreviations used:

DEB:	dystrophic epidermolysis bullosa
DEBRA:	Dystrophic Epidermolysis Bullosa Research Association
EB:	epidermolysis bullosa
EBS:	epidermolysis bullosa simplex
RDEB:	recessive dystrophic epidermolysis bullosa
SCC:	squamous cell carcinoma

From the Section of Dermatology[a] and Division of Infectious Diseases,[b] Department of Pediatrics, Hospital for Sick Children and University of Toronto; St Thomas Hospital and Great Ormond Street Hospital for Children, London[c]; Department of Obstetrics and Gynecology, Institute of Wound Research, University of Florida, Gainesville[d]; Biomedical Engineering, University of Alberta, Edmonton[e]; private practice, Toronto[f]; Clinical Research of the Blood and Marrow Transplantation Program and Stem Cell Institute, University of Minnesota, Minneapolis[g]; and Women's College Hospital and University of Toronto.[h]

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Reprint requests: Elena Pope, MD, MSc, Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G1X8 Canada. E-mail: Elena.pope@sickkids.ca.

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determined by the nature of mutations and the gene penetration resulting in different phenotypic expression.[2,3] In the absence of a cure, supportive wound care and early recognition and treatment of complications are the mainstays of patient treatment.

Wound care in the EB population poses unique challenges: clinical variability requires an individualized management plan; availability of a myriad of wound care products complicates the decision process and there is a high overall cost to the family and health units.

To date, there are no specific wound care guidelines or any evidence that address the wound care challenges of the EB population. The objective of this study was to generate a list of recommendations that will allow practitioners to better manage the complex needs of this population.

CAPSULE SUMMARY

- Wound care management is a mainstay of treating patients with epidermolysis bullosa, but currently there are no available guidelines.
- We generated 17 specific recommendations that include current evidence on wound care and address patient concerns.
- These recommendations should provide guidance to practitioners in providing wound care to patients with epidermolysis bullosa.

METHODS

A group of international experts in the fields of EB, wound care, infectious diseases, and bone-marrow transplantation met for 3 days in Alton, Ontario, Canada, to address wound care in patients with EB (Fig 1). The 11 attendees (physicians and nurses) were selected based on their EB clinical and research expertise and background in wound care, wound-healing biology, infectious diseases, and bone-marrow transplantation. Attendees were asked to review all the literature that pertained to their area of expertise and present their findings during the meeting. A group discussion ensued that generated a list of recommendations considered essential for enhancing wound healing in patients with EB. Using an online-based modified Delphi method for generating consensus,[4,5] the list was translated into a survey that was sent to 33 other international EB experts. The experts were asked to rate each recommendation on a 4-point Likert scale (strongly disagree, slightly disagree, slightly agree, strongly agree). At least an 80% agreement was required for each item to be adopted in the final list of recommendations.

RESULTS

Fourteen items (Table I) were generated through plenary discussion and sent for formal consensus. There were 15 respondents (45% response rate), with significant experience in the EB field (<1 year [13%]; 1-5 years [13%]; 6-10 years [7%]; 11-15 years [7%]; and >15 years [60%]). Most respondents were physicians (67%), while nursing (17%) and allied health professionals (7%) represented the difference. All items were retained because of a high degree of agreement with the original recommendations (Table I). The list was further refined by grouping items into main themes and specific recommendations (Table II).

Assess patient ability to heal and treat the cause

Recommendation 1: evaluate EB type–specific involvement. Patients with EB simplex (EBS) present predominantly with acral blisters exacerbated by heat and friction.[6] Blistering can be more extensive in the generalized forms of EBS and recessive forms of EBS with suprabasal cleavage.[6,7] Dowling-Meara form of EBS is characterized by grouped blisters that extend at the periphery resembling a string of pearls and acral blisters that lead to painful keratoderma. The Herlitz variant of junctional EB has a pathognomonic presentation with periorificial blistering, exuberant hypergranulation tissue, and periungual involvement with nail shedding. The diaper region is often particularly difficult to manage, as large denuded areas are difficult to protect from urine and feces. Scarring and milia formation are a hallmark of dystrophic EB (DEB). The location of the blisters is variable, but tends to affect trauma-prone areas. Patients with severe forms of recessive DEB (RDEB) commonly present with chronic wounds (lasting months, sometimes years) affecting large body surface areas.[8] Kindler syndrome is a rare autosomal recessive genodermatosis in which skin fragility early in life is gradually replaced by poikiloderma, scarring, and photosensitivity of the skin.[9]

Before deciding on a wound care management strategy it is important to take an inventory of the body surface area affected, and the types of skin involvement (intact blisters, erosions, chronic wounds). Ideal methods of serial assessment of wounds in patients with EB are lacking. In addition, most patients are very reluctant to expose their entire skin surface at each visit. Often the care team needs to negotiate a rotating skin examination schedule

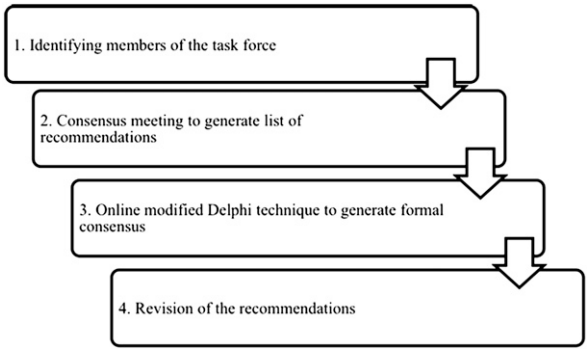

Fig 1. Methods diagram.

that allows for the entire skin surface to be carefully inspected at least every 6 months. Signs of local infection such as increased redness, local pain, odor, and exudate should be documented for each problematic wound.

Recommendation 2: consider patient age. The patient age is an important consideration when developing a wound care plan. Infants typically require a lot more control of their immediate environment to prevent trauma.[10] This includes, but is not limited to, techniques of gentle handling by the caregivers. Foam dressings are preferred for padding of bony prominences. The diaper area is particularly difficult to manage as it is prone to more physical and chemical trauma. The elastic bands of the diapers should be removed and cleansing wipes avoided. The diaper can be lined with a nonstick dressing or "buttered" with a thick layer of zinc oxide paste. As the child becomes more mobile, knee padding and soft special shoes are required to prevent blistering. Older patients tend to have more chronic ulcers that are critically colonized and infected and there is increased likelihood of colonization with antibiotic-resistant bacteria. Patients with more severe forms of EB are at an increased risk of squamous cell carcinoma (SCC). Although this is an unusual occurrence before the second or third decade of life,[11] it has been described in a 6-year-old child.[12]

Recommendation 3: assess and manage poor nutritional status. Wound healing can be delayed or interrupted in persons with existing comorbidities. Malnutrition is very common in the severe types of EB, resulting from a combination of reduced intake and increased demands.[13,14] Malnutrition leads to failure to thrive, delayed puberty, and anemia, a cascade of clinical and biological events, further affecting wound healing and increasing skin breakdown.[15-17] Low protein intake or relative deficiency can prevent the production of granulation tissue contributing to "stalled" healing.[18] Albumin levels, a gross indicator of long-term nutritional deficit, less than 2.0 to 3.0 g/dL (normal: 3.0-5.4 g/dL)[19] are associated with impaired healing. Blood sampling can be difficult as a result of poor venous access, therefore a more practical approach for assessing the overall nutritional status is monitoring of the growth curves in pediatric patients and body mass index in adults with EB. Regular nutritional consults (including calorimetry) to evaluate caloric needs are recommended. To optimize nutritional status, patients with severe forms of EB may require a gastrostomy tube. Supplementation of identified deficiencies is commonly suggested by many EB centers and 6- to 12-month monitoring to identify them is endorsed.

Recommendation 4: monitor and maintain hemoglobin levels above 80 g/L. Anemia, likely multifactorial in nature,[13] is a frequent and serious complication of the severe types of EB such as RDEB and junctional EB. Hemoglobin less than 100 g/L causes impaired wound healing in patients with venous ulcers as a result of decreased tissue oxygenation.[20] Low hemoglobin levels in patients with EB are one of the factors that may contribute to delayed healing. There is no ideal management strategy for dealing with anemia in patients with EB. A pathogenic-based approach is sensible, but not always possible. Adequate skin care and preventing/treating infection can minimize blood losses through the skin. Oral iron supplementation for correction of iron deficiency is widely used but its individual effectiveness varies. Moreover, gastrointestinal upset and constipation are reasons for nonadherence. Intravenous iron[21] plus erythropoietin were beneficial in a small study of patients with RDEB.[22] Blood transfusions should be considered for cases where hemoglobin levels are consistent below 80 g/L and/or for symptomatic patients who do not respond to other measures.

Patient-centered concerns

Recommendation 5: pain assessment and management. Pain is the most common symptom experienced by patients with EB, irrespective of subtype. The frequency and severity of pain is often proportional to disease severity, with up to 50% of patients with the most extensive type of EB (RDEB) experiencing daily pain greater than 5 (0-10 scale).[23] Although the cause of pain in EB is multifactorial, the skin and related EB lesions are by far the most significant source of pain. The pain can occur at rest from blisters and denuded skin, secondary infection, friction, and shearing with physical movements.[24] Pain can also be exacerbated during dressing changes, bathing, and other activities of daily living. Development of a pain management approach

Table I. Summary of formal consensus (modified Delphi technique)

Recommendations	"Somewhat agree" response, %	"Strongly agree" response, %	Consensus, %
A. Treat cause			
Assess patient ability to heal - Evaluate EB type−specific involvement and comorbidities - Consider patient age - Assess nutritional status - Monitor hemoglobin levels: ideally normal, minimally >80 g/L	11.8	82.4	94.2
Develop individualized goals and plan of care - Low hemoglobin consider: Iron supplementation, transfusions(s) - Low albumin: eg, protein supplements, feeding tube - Address other specific subtype involvement	0	94.1	94.1
B. Patient-centered concerns			
Address and support management of patient-centered concerns to enable healing: pain	13.3	86.7	100
Address and support management of patient-centered concerns to enable healing: itch	31.3	56.3	87.6
Address and support management of patient-centered concerns to enable healing: activities of daily living	13.3	80.0	93.3
Provide education and support to patient/parent and circle of care to increase adherence (coherence)	13.3	86.7	100
C. Local wound care			
Assess wound(s), location and characteristics	0.0	100.0	100.0
Gently cleanse wounds with low-toxicity solutions	33.3	66.7	100.0
Debridement	0.0	92.9	92.9
Assess and treat: - Superficial critical colonization and abnormal inflammation - Deep/surrounding tissue infection/generalized inflammation	7.1	92.9	100.0
Select dressing/topical therapy that is appropriate for needs of patient and caregiver	13.3	73.3	86.6
Evaluate expected rate of healing or reassess wound goals of care (including potential maintenance status)	26.7	73.3	100
Edge effect: if wound is stalled or edge/other area appear atypical, consider skin biopsy to rule out squamous cell carcinoma or other complications before considering active therapeutic options	26.7	73.3	100.0
D. Provide organizational support			
Consider health care system support structure including specialized nurses, interprofessional clinics, and structured approach to new cases	13.3	86.7	100.0

EB, Epidermolysis bullosa.

requires adequate documentation of pain levels before and after dressing changes, bathing, and other painful interventions.[25] Pain assessments using age-appropriate tools also allow identification of a temporal pattern and aggravating factors.[26,27] Other patient-related factors (anxiety, depression, past experiences) contributing to the pain experience should be recognized and treated. The approach to pain in a patient with EB includes preventative and therapeutic modalities (Table III). In general, wound-associated pain is both nociceptive, stimulus-dependent (gnawing, throbbing); and neuropathic, nonstimulus-dependent (burning, stinging, shooting, stabbing). Nociceptive pain is treated with the World Health Organization pain ladder medication (Table III).[28] Short-acting agents are used to determine the dose of longer-acting agents and for breakthrough pain before painful procedures. Neuropathic pain often responds to tricyclic agents, particularly second-generation agents. For nonresponders, gabapentin,[29] pregabalin, or other antiepileptics may be helpful. Procedural pain requires an interprofessional approach and communication to those within the circle of care. This is especially important for children with EB as they are often subjected to repeated procedures. Oral sucrose 24% is a useful, short-acting analgesic that is effective for children younger than 2 years of age.[30] For older children and adults, acetaminophen or morphine administered 30 minutes before the procedure may be used. Ketamine is another alternative drug that can also be used for

Table II. Wound care recommendations for persons with epidermolysis bullosa

Main themes	Specific recommendations
A. Treat cause (assessment and management of factors that impair healing)	1. Evaluate and manage EB type−specific involvement (simplex, junctional, dystrophic, Kindler syndrome) and comorbidities 2. Age-specific modification 3. Assess and address poor nutritional status 4. Monitor and correct hemoglobin levels
B. Patient-centered concerns	5. Evaluate and manage pain ◦ World Health Organization pain ladder for nociceptive pain ◦ Neuropathic pain: consider tricyclics, gabapentin, pregabalin ◦ Local or topical approaches ◦ Nonpharmacological approaches 6. Evaluate and manage of itch ◦ Combine nonsedating H-1 antihistamine in morning with sedating preparations at night ◦ Consider liquid quick-onset preparations for breakthrough (especially liquid formulations) 7. Identify and address limitations in ADL ◦ Consider rehabilitation consult 8. Provide education and support to patient/parent and circle of care to increase treatment adherence* a. Build confidence with patient and circle of care individuals, to increase adherence b. Develop interprofessional team c. Explore support from established EB centers • ebcare network (ebcarenetwork@lists.stanford.edu) • DEBRA foundations (www.debra-international.org; http://www.debra.org/international)
C. Local wound care	9. Assess wound(s) location and characteristics a. Location b. Target wound(s) c. Longest length × widest width at right angles d. MEASURE mnemonic 10. Gently cleanse wounds with low-toxicity solutions a. Saline, water, or acetic acid (0.25%-1.0%) b. Consider baths, whirlpool ± with salt, bleach, other antimicrobials 11. Debridement a. Drain blisters with sterile needle to prevent tracking, **but leave roof on blister** b. Consider nontraumatic conservative debridement of slough 12. Assess and treat a. Superficial critical colonization (NERDS) and abnormal inflammation b. Deep/surrounding tissue infection (STONEES)/generalized inflammation 13. Select appropriate dressing/topical therapy based on EB subtype a. Autolytic debridement: alginates, hydrogels b. Superficial critical colonization: silver, honey, PHMB c. Moisture balance foams with silicone coatings to prevent trauma and pain 14. Evaluate expected rate of healing or reassess wound goals of care 15. Evaluate edge effect ◦ If wound is stalled or edge/other areas appear atypical, consider skin biopsy to rule out squamous cell carcinoma or other complications before considering active therapeutic options ◦ Consider advanced or active therapies for healable but stalled wounds (skin grafts, living skin equivalents,† biological agents)
D. Develop individualized goals and plan of care	16. Develop/review periodically individualized plan tailored to: a. Patient unique biopsychosocial needs b. Patient preference

Continued

Table II. Cont'd

Main themes	Specific recommendations
E. Provide organizational support	17. Consider health care system support structure including specialized nurses, interprofessional clinics, and structured approach to new cases

ADL, Activities of daily living; *DEBRA*, Dystrophic Epidermolysis Bullosa Research Association; *EB*, epidermolysis bullosa; *PHMB*, polyhexamethylene biguanide.
*For professionals requiring further support contact DEBRA or other established EB centers.
†If cellular therapy candidate (identify early, especially junctional EB): use filtered blood products; consider theoretical risk of HLA sensitization with any cellular products (eg, allogeneic skin grafting); optimization of vaccine strategies for potentially immunocompromised individuals.

Table III. Pain management strategies

Pain management strategies	Goals/types	Actions
Preventative	Avoid trauma Avoid blister expansion Prevent local infection	• Protection, use foam dressings, use soft sleeping and seating surfaces • Clothing and shoe modification • Release fluid from blister, maintain roof of blister over affected area • Cover open areas • Control local colonization • Use of hand cleansers by caregivers before dressing changes
Therapeutic	Pharmacological	Nociceptive: • Mild pain: acetaminophen ± NSAIDs • Moderate pain: acetaminophen ± NSAIDs ± morphine • Severe pain: acetaminophen ± NSAIDs ± morphine/other strong opioids
	Nonpharmacological	Neuropathic: • Tricyclics (nortriptyline, desipramine, gabapentin, pregabalin, other antiepileptics • Relaxation/distraction • Biofeedback • Physical modalities (eg, vibration, cooling)

NSAIDs, nonsteroidal anti-inflammatory drugs.

dressing changes.[31] Nonpharmacological modalities (Table III) are also helpful in combination with the pharmacological measures listed above. Some potentially useful topical options include adding salt to the bathwater[32] and dressings with analgesics (Biatain-IBU, Coloplast, Humlebaek, Denmark).

Recommendation 6: control itch. Itch is a common symptom in the EB population, often poorly controlled, affecting quality of life. The exact mechanism is not known; abnormal persistent skin inflammation, overheating caused by dressings, local sensitizers,[33] and systemic opioids are potential contributors.[24] Management should start with a thorough history to identify the timing and exacerbating factors. Occasionally, changing the topical routine (discontinuation of dressings or topical antibiotics) may be sufficient. Itching at night may be related to body overheating and treated with sedating antihistamines (hydroxyzine) or a tricyclic with prominent H-1 antihistamine action (doxepin). Daytime pruritus may require a nonsedating antihistamine H-1 blocker (cetirizine, loratadine). Liquid preparations are always preferable as they have a shorter onset of action and are easier to swallow. There are anecdotal reports of successful use of ondansetron or low-dose gabapentin for persistent pruritus.[29]

Recommendation 7: recognize and address limitations in activities of daily living. Pain, odor, and mobility limitations have a significant impact on patients with EB and their daily living. The disease burden may include difficulties in performing personal care, engaging in school or employment activities, and increased financial burden.[34] Depression and anxiety are also common[35] and further contribute to social isolation. Fostering independence and safety during activities of daily living requires environmental modifications (special beds, seating in baths, wheelchairs, footwear). An early rehabilitation consult with frequent re-evaluations is recommended.

Recommendation 8: provide education and support to the patient/parent and circle of care to increase treatment adherence. Development

Table IV. Dressing choices according to indications/type of wounds

Type of wound/ indication	Primary dressing	Secondary dressing	Topical therapy
Protection	Foams Modified absorbent pads Lipidocolloid dressings Contact layers	Burn net to keep in place (if feasible)	None
Open nonexudative	Foams Modified absorbent pads Lipidocolloid dressings Contact layers	Burn net to keep in place (if feasible)	None
Exudative	Foams Lipidocolloid dressings Hydrofibers	Burn net to keep in place (if feasible)	Topical antibiotics (avoid allergens)
Eschar	Hydrogels Biosynthetic cellulose Hydrocolloids	Foams Modified absorbent pads	None
Critically colonized or infected	Contact layer Hydrofibers Alginates Antimicrobials	Foams Modified absorbent pads	Topical antibiotics (avoid allergens)
Painful	Biosynthetic cellulose Hydrogel sheets	Foams Modified absorbent pads	Topical NSAIDs
Itchy	Biosynthetic cellulose Hydrogel sheets	Foams Modified absorbent pads	Short course of topical midpotency corticosteroids
Hypergranulation	Contact layer with antimicrobial, anti-inflammatory	Foams Modified absorbent pads	Short course of topical potent corticosteroids, beware of infection

NSAIDs, nonsteroidal anti-inflammatory drugs.

of a therapeutic relationship involves appropriate support and education. This occurs when trust, communication, and open dialogue allow patients and their caregivers to understand that each involved person has a meaningful contribution in the decision-making process. EB is a complex multisystem disease; therefore communication among various health care professionals is paramount. A centralized, interprofessional approach with care coordination including open communication with the general practitioner and home-care team is the most effective way of caring for these patients. The burden of caring for these patients is taxing for health teams. As not all patients can be looked after in specialized centers, non-EB practitioners should seek support from established EB centers, EB care network, or Dystrophic Epidermolysis Bullosa Research Association (DEBRA) foundations.

Local wound care

Recommendation 9: assess wound locations and characteristics. The first step is to create an inventory of the body surface area involved and the type of wounds (intact blisters, erosions/ulcers, chronic, exudative vs nonexudative wounds). There are very limited tools available for determining the extent of skin involvement. The palm method, used for patients with burn,[36] is not always feasible. Digital photography may be helpful particularly for assessing and monitoring the progress of problematic lesions. Another objective method is the MEASURE[37] paradigm used for assessment of chronic wounds (measure size; exudate [amount and characteristics]; appearance [base or granulation tissue]; suffering [pain]; undermining [depth measured in centimeters]; re-evaluate; and edge). We propose using this paradigm for patients with EB (by eliminating the undermining and allocating suffering SU rather than S) in nonhealing wounds for developing a wound care plan and monitoring the response over time. The wound care decision approach should consider the wound location, need for extra padding and protection, specialized dressings, and feasibility for everyday use (Tables IV to VI).

Recommendation 10: gently cleanse wounds with low-toxicity solutions. The standard of care for wound cleansing is to use solutions that are gentle and noncytotoxic.[38] For patients with EB we recommend gentle cleansing with a saline solution, water, or dermol 500 (containing benzalkonium chloride 0.1%,

Table V. Dressings categories, properties, indications

Dressing type	Commercial name	Proposed scientific mechanism of action/precautions	Expert comment (opinion)
Foams	Mepilex* Mepilex lite* Mepilex border* Mepilex border lite* PolyMem†	Some contain silicone layer to make these nonadherent Generally made from hydrophilic polyurethane Nonocclusive Semipermeable surface allows exudate into dressing and foam traps moisture	Allow large amounts of fluid and wound drainage to be absorbed Provide padding and protection to wounds Depending on amount of exudate, can be left in place up to 7 d Some require secondary dressing to hold in place Bordered dressing may sometimes be too sticky and should be used with caution
Hydrogels	Gels: Duoderm‡ Intrasite§ Sheets (cool dressings): ActiFoamCool‖ Intrasite Conformable§	Made of insoluble polymers that expand in water and hydrate wounds Provide autolytic debridement	For wounds with minimal or no exudate Because of hydrating capacity, these offer cooling effect and may aid in relief of pain, itch, and discomfort
Alginates (calcium or calcium/sodium)	Kaltostat‡	Made of nonwoven fibers derived from seaweed Turn into nonsticky gel when in contact with wound drainage	Requires exudate Does not work on dry wounds or wounds with eschar Calcium alginate dressings release calcium ions that help stop bleeding
Hydrofibers	Aquacel‡	Made of sodium carboxymethyl-cellulose that, when in contact with wound drainage, becomes gel and provides moist environment	More absorbent than alginates Consider in wounds with heavy drainage
Modified absorbent pads	Telfa¶ Restore# ETE* Mesorb*	Thin layer of absorbent cotton fibers that are enclosed in sleeve of perforated polyethylene terephthalate and sealed along two edges Plastic film prevents dressing from adhering to wound surface and perforated surface allows passage of exudate into pad	Relatively inexpensive and nonadherent If there is significant bleeding or exudate, dressing will adhere
Contact layers	Mepitel* Silflex** Mepitac* Adaptic touch†† Siltape or Silflex**	Protective, inert material that allows nontraumatic removal	
Biosynthetic cellulose	Suprasorb X‖	Dressing consisting of cellulose, water, and 0.085% chlorhexidine gluconate (preservative) that has ability to both absorb and donate moisture	Also considered cooling dressing, aids in pain reduction and adding moisture to wounds May also reduce itch

Continued

Table V. Cont'd

Dressing type	Commercial name	Proposed scientific mechanism of action/precautions	Expert comment (opinion)
Lipidocolloid dressings	Urgotul[‡‡] Restore[#] (North American equivalent to Urgotul)	Composed of open-weave polyester mesh impregnated with hydrocolloid polymers dispersed within petrolatum When in contact with exudate, hydrocolloid polymers are hydrated and constitute with petrolatum lipidocolloid interface that provides nonadherent surface	For wounds with exudate Also used for protection of vulnerable areas

*Molnlycke Health Care, Gothenburg, Sweden.
†Ferris Manufacturing, Burr Ridge, IL.
‡ConvaTec, Skillman, NJ.
§Smith and Nephew, London, UK.
‖Activa Healthcare, Staffordshire, UK.
¶Kendall Company Ltd, Mansfield, MA.
#Hollister, Libertyville, IL.
**Advancis Medical, Oxfordshire, UK.
††Systagenix, Gatwick, West Sussex, UK.
‡‡Urgo, Shepshed, Longhborough, UK.

chlorhexidine hydrochloride 0.1%). Avoidance/short-term use of cytotoxic solutions (Dakin, Century Pharmaceuticals Inc, Indianapolis, IN, and povidone-iodine) is prudent because of skin fragility and pain associated with open wounds. Soaking of each individual wound for 5 to 10 minutes or removing the dressings in the bathtub may help reduce pain and trauma associated with dressing changes. A dilute acetic solution (5% white vinegar diluted to 0.25%-1.0%) or bleach (5-10 mL in 5 L of water) may decrease the bacterial carriage.[39] Bathing facilitates cleansing, nontraumatic dressing removal, and supplemental antibacterial control (using diluted acetic acid or bleach) and is better tolerated than showering.[32]

Recommendation 11: blister management and gentle debridement of eschar/slough. New blister formation is the hallmark of EB. To prevent blister extension we recommend puncturing it (at multiple sites to facilitate optimal drainage) with a sterile needle to release the inner fluid. The overlying skin is left in place, acting as a biological dressing, reducing pain, and minimizing infection risk. A firm dehydrated eschar or soft slough requires debridement to remove senescent cells that are deficient in cellular activities and biofilms that maintain the inflammatory process.[40] Debridement in the EB population should, whenever possible, involve nonphysical methods (hydrogel, calcium alginate dressings).

Recommendation 12: assess and treat critical colonization, infection, and abnormal inflammation. Inflammation or infection impairs normal healing. The difference between colonization and infection is the interplay between the number and type of colonies and host resistance.[41] In bacterial colonization, bacterial colonies do not interfere with healing. Critical colonization occurs when the bacterial proliferation causes local damage and wounds get "stuck" precluding healing. Surface critical colonization and deep and surrounding skin infection are clinical diagnoses. The mnemonics NERDS (nonhealing; increased exudate; red, friable tissue; debris, dead slough; smell) and STONEES (increased size; temperature >3°F warmer than contralateral skin; os, exposed/probing to bone; new areas of breakdown; erythema/edema of surrounding skin; increased exudate and smell)[42,43] represent the two levels of superficial bacterial damage or deep and surrounding skin infection and have been validated for use in chronic wounds. Any 3 NERDS criteria are indicative of superficial critical colonization and require a topical antimicrobial. Three or more criteria from STONEES suggest deeper/surrounding skin infection and need for systemic therapy. Although these concepts need to be validated for EB, more than 3 criteria are useful to distinguish infection from persistent inflammation. The most common bacteria isolated from chronic

Table VI. Dressing choices/topical therapy for special locations/indications

Location	Dressing/topical therapy	Properties	Expert comment (opinion)
Perianal area	Restore contact layer*	Autolytic debridement Provides moisture	Difficult to keep in place Can be used to line diaper
	Intrasite conformable†	Autolytic debridement Provides moisture	Difficult to keep in place Can be used to line diaper
	Bepanthen (ointment with pro-vitamin B5)‡	Aids in moisture balance	
	Cavilon (liquid barrier film)§	Creates breathable, transparent coating on skin	Does not sting Alcohol free
	Emollin 50/50 emollient spray (white soft paraffin and liquid paraffin)‖	Water repellent Provides barrier protection	Does not sting
Oral mucosa	BioXtra (salivary substitute)¶	Provides moisture	
	Difflam spray (active ingredient is benzydamine hydrochloride, a NSAID)#	Reduces pain and inflammation Also acts as local anesthetic	
	Corsodyl (mouthwash containing chlorhexidine)#	Provides antiseptic and disinfectant properties	
	Gelclair (bioadherent oral gel)**	Creates barrier that protects nerve endings, reducing pain	Can be used before meals
Feeding tube sites	AMD-PHMB foam fenestrated disc dressing (antimicrobial foam dressing)††	Moisture balance Contains antiseptic (PHMB) (effective against MRSA, VRE, gram-positive and gram-negative bacteria, fungi, and yeast)	
	4% Sucralfate mixed with Cavilon§	Protectant	
PC/C lines	Mepitac*, Adaptic touch‡‡, Siltape§§, or Silflex§§	Nonstick	
Adhesives	Medical adhesive remover Appeel‖‖ or Niltac¶¶ Adhesive remover spray***		Adhesive remover is temporary These sprays are silicone based
Retention bandage	Acti-Wrap cohesive retention bandage†††	Secures dressings in place	Useful to fix small dressings

AMD, Advanced micro devices; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *NSAID*, nonsteroidal anti-inflammatory drug; *PC/C*, percutaneous catheter; *PHMB*, polyhexamethylene biguanide; *VRE*, vancomycin resistant enterococcus.
*Molnlycke Health Care, Gothenburg, Sweden.
†Smith and Nephew, London, UK.
‡Bayer Health Care, Wayne, NJ.
§3M, St. Paul, MN.
‖CD Medical Ltd, Derbyshire, UK.
¶Lighthouse Health Products, Cambridge, Ontario, Canada.
#Glaxosmithkline Consumer, Brentford, UK.
**Helsinn Healthcare, SA, Pazzallo, Switzerland.
††Kendall Company Ltd, Mansfield, MA.
‡‡Systagenix, Gatwick, West Sussex, UK.
§§W M Bamford Co & Ltd, Lower Hutt, New Zealand.
‖‖CliniMed Ltd, Bucks, UK.
¶¶Trio Health International Ltd, Great Missenden, Buckinghamshire, UK.
***Humlebaek, Denmark.
†††Active Healthcare, Staffordshire, UK.

and most likely EB wounds are gram-positive organisms (*Staphylococcus aureus* and *Streptococci* species), gram negatives (*Pseudomonas aeruginosa*), and anaerobes (R. G. Sibbald, MD, oral communication, July 2012). As such, documentation of critical colonization/infection in the EB population is rarely needed and skin swabs are indicated only to determine antibiotic selection in cases of multiresistant organisms or nonresponsive infection.

Critical colonization can be controlled with topical agents. The bacterial load may be reduced by bathing with diluted bleach, applying compresses, or

using sprays with diluted vinegar.[39] Lipid-stabilized hydrogen peroxide cream (Crystacide, DermaUK, Stotfold, UK) is well tolerated and effective when applied directly on the wound or contact dressing.[39] Topical antibiotics/antimicrobials (eg, polymyxin B-gramicidin, fusidic acid, mupirocin, silver sulfadiazine) should be used only for short periods of time and rotated every 2 to 6 weeks to prevent resistance and sensitization.[39] When using these agents, we recommend applying them on the dressing rather than directly on the skin to limit pain and trauma. Other options include dressings containing silver, honey, iodine, and polyhexamethylene biguanide (Table V).[44] Silver has broad-spectrum antimicrobial activity and must be ionized to exert maximum effect. Ionized silver requires an aqueous or water environment.[44] High serum levels of silver have been documented in patients with EB who use silver dressings (J. Mellerio, MD, oral communication, July 2011); therefore, their prolonged use over large surface areas should be discouraged. Medical-grade honey products (ointments, dressings) may provide short-term benefit, but their use can increase local pain and may temporarily increase exudate levels.[39] The use of antimicrobial dressings should be reviewed at regular intervals, and discontinued if critical colonization has been corrected or if there is no beneficial effect.

Signs of deep and surrounding tissue infection (lymphadenopathy, fever, and malaise) require systemic antimicrobial therapy. Empirical use of systemic antibiotics that cover common pathogens is recommended. The antibiotic choice can be further refined based on identified pathogenic organisms and their antimicrobial sensitivities. *Streptococcus pyogenes* presence requires treatment even in the absence of overt clinical infection because of risk of complications. For chronic nonhealing wounds, long-term, alternating, low-dose antibacterial agents (trimethoprim, macrolides, doxycycline) may be beneficial for their anti-inflammatory effects.

Recommendation 13: select a dressing/topical therapy that is appropriate for the needs of the patient and the caregiver based on the subtype of EB. Dressing choices should be individualized based on EB subtype, extent and wound location, dressing frequency, cost, and availability (Tables IV to VI). Wound healing requires an appropriate wound surface moisture balance. This is achieved by using dressings with occlusive, semi-occlusive, absorptive, hydrating, and hemostatic characteristics, depending on the wound characteristics and drainage (Tables IV to VI). Another consideration for the EB population is management of chronic wounds. Chronic wounds are often stalled in the inflammatory stage.[44] These wounds demonstrate marked increased activity of inflammatory cells and associated mediators such as matrix metalloproteinase and elastase,[44] responsible for degradation of extracellular matrix and growth factors that hinder progression toward re-epithelialization.[45] Combined local and systemic intervention may be required to facilitate wound healing (recommendation 12).

Recommendation 14: evaluate the expected rate of healing or reassess wound goals of care (including potential maintenance status). A wound size reduction of 20% to 40% in 2 and 4 weeks is quoted to be a reliable predictor of healing at 12 weeks.[46-48] In addition, clinical observation of the edge of the wound is foretelling: nonhealing wounds often have a "cliff edge" instead of the purple "tapered sandy shore beach" of healable ones. If the wound edge is not advancing after appropriate wound-bed preparation, advanced therapies should be considered[49] after all causes of delayed healing have been ruled out (SCC). Complete healing may not be an achievable goal in EB. Other wound-related outcomes such as pain reduction, decreased bacterial load, and need for dressing changes, or increased quality of life are more attainable.

Recommendation 15: edge effect—if a wound is stalled, the edge or other areas appear atypical; consider a skin biopsy to rule out SCC or other complications before considering active therapeutic options. The cumulative risk of developing SCC in severe generalized RDEB by age 55 years is 90%[8] representing a major cause of morbidity and mortality.[11] They tend to occur much earlier in the EB population, are multifocal, and more aggressive. As wound chronicity is the norm in many patients with EB, a high degree of suspicion is required. Biopsy of wounds that enlarge rapidly, have increased pain, change in appearance on serial photographic documentation, or "feel different" is recommended.[50]

Develop individualized goals and plan of care

Recommendation 16: develop and reassess tailored plan of care. A comprehensive assessment should result in an individualized wound care plan tailored to the individual, taking into consideration unique biopsychosocial needs (Table VII). Patient preference must be respected and reflected in the wound care plan.[51] It is common for EB families to have time-tested routines that do not necessarily follow the currently accepted medical wisdom. A flexible approach will most likely increase adherence, increase satisfaction with care, and lead to improved outcomes. With the new, disease-modifying cellular therapies that are

Table VII. Considerations for addressing biopsychosocial needs

Biopsychosocial need	Considerations
Individual personal preferences	• Reflect, respect. and integrate experiences and feedback from patient and those in circle of care
Risk factor	• EB subtype
Comorbidities	• Anemia • Malnutrition • Cardiomyopathy
Quality-of-life issues	• Frequency of dressing changes • Pain management • Interference with daily activities • Schooling and/or employment
Support systems/ circle of care	• Consider who performs skin care • Access to home care • Specialized EB teams
Access to care	• Specialized EB interprofessional team

EB, Epidermolysis bullosa.

Table VIII. Care principles for potential candidates to cellular therapies (eg, stem cell transplantation)

Principles	Actions
Maintain overall health by preventing, recognizing, and treating disease-related complications	• Monitoring and treatment of anemia • Monitoring and correction of malnutrition • Monitoring and treatment of cardiomyopathy
Minimize risks of exposure to antibodies	• Use filtered blood products • Consider risks of HLA exposure with cellular products (eg, allogeneic skin grafting)
Optimize vaccination strategies for potentially immune-compromised individuals	• Ensure compliance with vaccination schedule before procedure

currently emerging,[52] it is also important to maximize the chances of each patient being a potential candidate for these therapies (Table VIII). The wound care plan should be clearly outlined in a written document given to the family and copied to the family practitioner and home-care personnel. The care plan should also be evaluated and updated regularly.

Provide organizational support

Recommendation 17: consider a health care system support structure including specialized nurses, interprofessional clinics, and a structured approach to new cases. EB is not just a skin disorder; therefore treating a patient with EB requires involvement of a dedicated team with expertise in all aspects of care. Over the past decade specialized EB clinics have opened in 16 countries worldwide, providing an interprofessional model of care with input from many allied health professionals (eg, nurses, physicians, surgeons, occupational therapists, physical therapists, social workers, dietitian, music therapists).[53-67] Isolated cases can be overwhelming to health practitioners particularly when referral to an established EB center is not feasible. Access to international EB experts via http://www.internationalebforum.org is possible and has changed the fabric of pre-existing professional isolation. Other resources for patients and practitioners are DEBRA foundations that exist in many countries.

The birth of a child with EB is a traumatic event for a family. We have found that early education about the disease, determining the type/subtype of EB as soon as possible, and providing ongoing support from knowledgeable practitioners allows a family to regroup and focus on providing the best care to their baby.

DISCUSSION

EB is one of the most complex diseases in medicine, with severe EB types having devastating effects on the quality of life and life span of affected patients. Until a cure is available, anticipatory guidance for possible disease-related complications and appropriate wound care are the cornerstones of EB management. EB is a prototype of an orphan disease. Although rare, its severity combined with little evidence for clinical practice leads to suboptimal patient care and practitioner isolation. Practice guidelines (systematic statements that assist physician in decision making)[68] are increasingly recognized as tools that reduce inappropriate care, control geographic variation, and make use of best health care resources.[69] To date there is no randomized controlled trial scientific evidence for any of the health care interventions that we use in these patients. To our knowledge, this is the first attempt to develop guidelines of care for the EB population that focus on wound care, with a holistic approach that takes into account other patient-related factors, patient preferences, and the immediate and extended care teams. We have brought together experts in the fields of EB, wound care biology, and clinical practice to provide the best available approaches to optimize wound care in patients with EB. The next step is to seek further consensus on specific statements that make up each recommendation. These

guidelines need to be periodically renewed to reflect new scientific and clinical practice knowledge.

International experts

Edward Barrett (Canada), Anna Bruckner (United States), Maya El Hachem (Italy), Louise Fret-Lalonde (Canada), Gerry Kelly-Mancuso (United States), Michelle Lee (Canada), Andrew Lin (Canada), Anne Lucky (United States), Celia Moss (United Kingdom), Dedee Murrell (Australia), Annmarie Ormonde (Italy), Francis Pallison (Chile), Agnes Schwieger (Germany), Rosemarie Watson (Ireland), Karen Wiss (United States).

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